

Brief report

## Magnesium oxide augmentation of verapamil maintenance therapy in mania

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### Abstract

The authors compared the antimanic effects of a verapamil–magnesium oxide (V–M) combination with a verapamil–placebo combination (V–P) in patients pretreated with verapamil. BPRS scores and serum magnesium levels were compared. The V–M combination was found to be significantly more effective than V–P in reducing manic symptoms ( $P = 0.015$ ). Serum magnesium levels were significantly higher in the V–M group ( $P < 0.04$ ). These data suggest that magnesium may increase antimanic efficacy of verapamil by mechanisms which may operate at the intracellular level. The magnesium–verapamil combination may have clinical application as an adjunct to verapamil in the maintenance therapy of mania. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Bipolar disorder; Calcium; Calcium channel; Calmagnite; Lithium

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### 1. Introduction

Verapamil is an antiarrhythmic agent which blocks calcium influx through slow channels in the myocardial cells. It is therefore used to treat

cardiovascular diseases including angina, supra-ventricular arrhythmias and hypertension. It has also been used as an antimanic agent (Giannini et al., 1984).

Verapamil shares many pharmacological properties with lithium, the standard treatment for acute and chronic mania. At the cellular level, both block adenyl cyclase activity, inhibit sodium–calcium counter-exchange and reduce

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calmodulin activity. At tissue and organ levels, these medications inhibit TSH release and ADH signaling in the kidney (Packer and Frishman, 1982).

In addition to shared properties with lithium, verapamil has several unique properties which make it a potentially attractive antimanic agent. It inhibits excitation–secretion coupling at adrenergic synapses (Hoschl, 1990) and antagonizes both dopaminergic and serotonergic receptors (Chou, 1991). Verapamil does not require frequent serum levels. While long-term lithium therapy may be associated with renal damage or inhibition of thyroid and parathyroid hormone release, verapamil has no similar long-term side effects (Hoschl et al., 1986).

Because of these advantages, verapamil was indeed employed as an antimanic agent within 10 years after its introduction. After initial case reports (Dubovsky et al., 1982; Hoschl et al., 1982), verapamil was compared favorably with lithium in a single-factor repeated-measure design (Giannini et al., 1984). Similar favorable results were found in double-blind studies when verapamil was compared to placebo (Dubovsky et al., 1981), lithium carbonate (Garza-Trevino et al., 1982), chlorpromazine (Hoschl and Kozeny, 1989), valproic acid (Giannini et al., 1989) and clonidine (Giannini et al., 1985).

In contradistinction, other studies have reported less efficacious responses to verapamil. In double-blind crossover studies, patients pretreated with lithium (Giannini et al., 1987) or resistant to it (Barton and Gitlin, 1987) had diminished antimanic responses to verapamil. A randomized single-blind trial compared lithium to verapamil and reported verapamil to be inferior (Walton et al., 1996) to lithium. Another placebo-controlled trial showed no benefit of verapamil over placebo (Janicak et al., 1998). Also there is some question as to whether a sufficient fraction of verapamil crosses the blood–brain barrier to be considered a viable psychoactive drug.

Combining lithium therapy with verapamil therapy for refractory manic patients may not be a treatment option. This combination has been reported to produce neurotoxicity (Price and Gi-

annini, 1986). Another possible combinant with verapamil is magnesium ion. Magnesium shares some potential antimanic effects with verapamil. It inhibits calcium activity at calmodulin and at calcium channels, producing membrane stability (Hoschl and Kozeny, 1990). It also inhibits calcium-mediated neurotransmitter release (Walton et al., 1996) and may alter the configuration of post-synaptic receptors (El-Malakh and Juzirs, 1990; Chou, 1991). Magnesium therapy in alcohol-induced hypomagnesemia during alcohol withdrawal reduces some manic-like symptoms (Giannini, 1998). However, antimanic activity of verapamil is not associated with changes in serum magnesium levels (Goodnick, 1995).

Between 20 and 40% of manic patients are unable to tolerate side effects of lithium therapy or are unresponsive to it (Packer and Frishman, 1982; Barton and Gitlin, 1987). Therefore alternative therapeutic regimens are needed. Verapamil is one such candidate but, unfortunately, has many side effects. Higher doses of verapamil may produce hypertension, bradycardia, pulmonary edema and AV block in small population segments. In order to avoid such side effects, it was hypothesized that combining magnesium therapy with verapamil therapy could produce significant antimanic effects at lower verapamil dosages (Delhumeau et al., 1995).

A search of the world literature revealed no reported adverse interaction between verapamil and magnesium oxide or other formulations of magnesium. Therefore, we decided to study the efficacy of combined magnesium–verapamil therapy.

## 2. Methods

Twenty white male volunteers, seen in a private clinic, had met DSM-IV criteria for prior manic episodes and were currently receiving verapamil maintenance therapy. All patients had been receiving verapamil for durations ranging from 6 months to 2 years before joining the study. The ages ranged from 22 to 30. All were told that they would receive a number of unspecified antimanic

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